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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,432	03/31/2004	Thomas E. Wagner	035879-0182	3800

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
09/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/813,432	**Applicant(s)** WAGNER ET AL.	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 September 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3,10-16 and 18*.
   Claim(s) withdrawn from consideration: *5-9*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 9/06/2007 in response to the previous Final Office Action (06/06/2007) is acknowledged and has been entered.

Claims 1-3, 5-16 and 18 are pending.

Claims 5-9 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-3, 10-16 and 18 are currently under consideration.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 3 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS).

Terman teaches a pharmaceutical composition comprising a carrier, a superantigen and an immunotherapeutic antigen (column 15, line 40 to column 16, line 4). With regards to the immunotherapeutic antigen, the patent teaches (column 8, lines 1-12 and column 50, lines 10-14) that the immunotherapeutic antigens include, but are not limited to, galactose-1-3-galactose which

elicits an acute-phase hyperimmune response. The patent further teaches (column 50, lines 48-54) that the immunotherapeutic antigen, e.g., galactose-1,3-galactose, can be modified with a monoclonal antibody to generate an antigen-antibody conjugate which specifically targets the cell surface of tumor cells.

Terman does not explicitly teach that the immunotherapeutic antigen can comprises a targeting peptide, wherein the targeting peptide comprises asparagine-glycine-arginine (NGR).

Rouslahti et al. teach tumor homing molecules comprising an NGR peptide motif, as well as NGR peptide conjugates (column 3, lines 1-10). Specifically, Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumors, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues (column 1, liens 60 to column 2, lines 24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an NGR targeting peptide for the monoclonal antibody taught by Terman in view of Rouslahti et al. One would have been motivated to do so because Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumor, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would achieve a pharmaceutical composition which targets the tumor vasculature and not the tumor cell surface.

In response to this rejection, Applicants assert that present claims are directed to a pharmaceutical composition comprising (a) a carrier portion, (b) a targeting portion, wherein said targeting portion comprises a targeting peptide that targets cancer cells, tumor vasculature or neovasculatorure, and (c) an immune response triggering portion, wherein said immune response triggering portion is glactose-a-1,3-galactose which triggers complement mediated hyperacute immune response, and wherein neither the carrier portion of (a) or the targeting portion of (b) is an antibody or antibody fragments. As such, Applicants assert that the combination of cited references do not arrive at the claimed invention, nor do they provide the surprising result that antibody-targeting actually inhibits the complement-mediated hyperacute immune response; and therefore,

can not render the claimed invention obvious. For example, Applicants assert that to combine Ruoslahti with Terman and arrive at the present invention, not only would one have to substitute the targeting moiety of Terman, but also one of skill would be required to delete the super antigen portion of the Terman complex because the use of superantigens such as enterotoxins induces a T cell mediated response which is different from the instant invention which uses a complemented-mediated hyperacute immune response. Thus, Applicants assert that a person of skill in the art would have no reason to delete this important portion of the Terman complex and Ruoslahti provides no such incentive to remove the superantigen as it merely discloses the NGR peptide. Moreover, Applicants assert that the claimed limitation that neither the carrier nor the targeting portion can be antibody-derived is critical to the instant invention as it has been surprisingly found that the use of an antibody in the present invention inhibits the complement mediated hyperacute immune response, as discussed in Example 3, specifically paragraph 61 of the specification and shown in the data of Figure 2. Thus, Applicants assert that while Terman speculates that the use of antibody-targeting in conjunction with the galactose-a-1,3-galactose-superantigen complex would trigger the hyperacute rejection process as an additive effect of T cell stimulation, Terman does not provide any data showing such an effect; and therefore, a person of skill in the art, reading Terman, would conclude that using an antibody to target galactose-a-1,3-galactose complexes would be successful, when Applicants have clearly shown that it would not be.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments, the Examiner acknowledges and recognizes that the instant claims encompass a pharmaceutical composition **comprising:** (a) a carrier portion, (b) a targeting portion, wherein said targeting portion comprises a targeting peptide that targets cancer cells, tumor vasculature or neovasculatorure, and (c) an immune response triggering portion. Thus, the transition phrase comprising which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As such, the instant claims do not appear to exclude the addition of a super antigen. Similarly, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)

(motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005). As noted above, Terman teaches a pharmaceutical composition comprising a carrier, a superantigen and an immunotherapeutic antigen, wherein the immunotherapeutic antigen, e.g., galactose-1,3-galactose, can be modified with a monoclonal antibody to generate an antigen-antibody conjugate which specifically targets the cell surface of tumor cells, whereas Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumors, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would achieve a pharmaceutical composition which targets the tumor vasculature and not the tumor cell surface. Furthermore, as admitted by Applicants in the prior response, "adding the NGR peptide to the immunotherapy-superantigen complex of Terman would still activate the T-cell mediated immune response". As such, the reasonable expectation of success is high. Thus, for the reasons set forth above, Claims 1 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS).

Claim 2 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and in further view of Corti (WO 01/61017, 2001, IDS).

Terman in view of Rouslahti et al. teach, as applied to claims 1 and 3 above, a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the carrier, Terman et al. teach that the carriers include, but are not limited to, serum albumin (column 15, lines 25-31).

Terman in view of Rouslahti et al. do not explicitly teach that the serum albumin carrier is human serum albumin.

Corti teaches a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion, wherein the carrier portion is human serum albumin, the targeting portion is a peptide comprising a NGR motif, and the immune response triggering portion is TNF (page 6, line 27 to page 7, line 7 and page 15, lines1-10). Specifically, Corti teaches that the anti-tumor activity was not changed by the addition of human serum albumin to TNF and NGR-TNF solutions, as the carrier (page 15, lines 1-3)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use human serum albumin as the carrier in the composition taught by Terman and Rouslahti et al. in view of Corti. One would have been motivated to do so because Corti teaches that the anti-tumor activity of TNF was not changed by the addition of human serum as the carrier. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would not change the anti-tumor activity of the pharmaceutical composition.

In response to this rejection, Applicants assert that the teachings of Corti et al. do nto remedy the deficiencies of the complexes of Terman and Ruoslahti as it merely specifies the type of carrier to be used. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above, e.g., Terman and Ruoslahti response.

Claims 10-16 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and in further view of Patierno et al. (US 6,288,039).

Terman in view of Rouslahti et al. teach, as applied to claims 1 and 3 above, a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the NGR peptide motif, Rouslahti et al. teach that the NGR peptide motif specifically homes in vivo to breast tumor, melanoma, as well as, Kaposi's sarcoma (column 17, line 65 to column 18, line 2). In addition to the NGR peptides,

Rouslahti et al. teach that aminopeptidase inhibitors such as bestatin can be used for directing a moiety to the angiogenic vasculature of a tumor (column 3, lines 5-10).

Terman in view of Rouslahti et al. do not explicitly teach a kit comprising, in a suitable container, a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion.

Patierno et al. teach pharmaceutical compositions and kits for treating and diagnosing breast cancer (abstract). Specifically, the reference teaches a kit for treating breast cancer comprising a therapeutically effective amount of an inhibitor in a pharmaceutically acceptable carrier and a device for delivering the inhibitor to the breast cancer, wherein the carrier and device are packaged in a container (column 7, liens 61-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the pharmaceutical composition as taught by Terman and Rouslahti et al. as a kit in view of the Patierno et al.. One would have been motivated to do so because standard kits enhance the probability of the reproducibility and efficiency of the treatment process and further provide for increased marketability, convenience, reliability, and economy. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by packaging the pharmaceutical composition taught by Terman and Rouslahti et al. as a kit, one would achieve a convenient and reliable kit which can be used for the treatment of breast cancer.

In response to this rejection, Applicants assert that the teachings of Patierno do not remedy the deficiencies of the complexes of Terman and Ruoslahti as it merely discloses kits and does not teach compositions that trigger a complement mediated immune response. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above, e.g., Terman and Ruoslahti response.

Claim 18 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and Patierno et al. (US 6,288,039) and in further view of Corti (WO 01/61017, 2001, IDS).

Terman in view of Rouslahti et al. and Patierno et al. teach, as applied to claims 10-16 above, a kit in a suitable container comprising a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the carrier, Terman et al. teach that the carriers include, but are not limited to, serum albumin (column 15, lines 25-31).

Terman in view of Rouslahti et al. and Patierno et al. do not explicitly teach that the kit comprises human serum albumin as the carrier.

Corti teaches a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion, wherein the carrier portion is human serum albumin, the targeting portion is a peptide comprising a NGR motif, and the immune response triggering portion is TNF (page 6, line 27 to page 7, line 7 and page 15, lines1-10). Specifically, Corti teaches that the anti-tumor activity was not changed by the addition of human serum albumin to TNF and NGR-TNF solutions, as the carrier (page 15, lines 1-3)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use human serum albumin as the carrier in the kit taught by Terman, Rouslahti et al. and Patierno et al. in view of Corti. One would have been motivated to do so because Corti teaches that the anti-tumor activity of TNF was not changed by the addition of human serum albumin as the carrier. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would not change the anti-tumor activity of the pharmaceutical composition.

In response to this rejection, Applicants assert for the same reasons stated above, the teachings of Corti and Patierno do not remedy the deficiencies of the complexes of Terman and Ruoslahti. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above, e.g., Terman and Ruoslahti response.

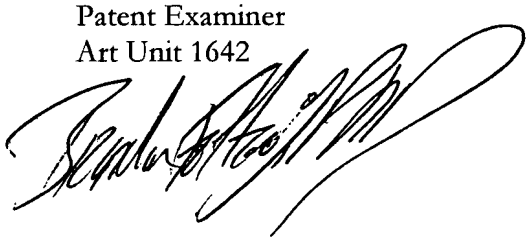
Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642



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